DOI:10.3872/j.issn.1007-385x.2018.04.019

·综 述·

间变性淋巴瘤激酶基因阳性的晚期非小细胞肺癌脑转移的靶向治疗进展

Progress in targeted therapy of anaplastic lymphoma kinase gene positive non-small cell lung cancer with brain metastasis

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[摘 要] 间变性淋巴瘤激酶(anaplastic lymphoma kinase,*ALK*)基因重排是发生非小细胞肺癌(non-small cell lung cancer,NSCLC)的重要致癌驱动因素之一,*ALK*阳性的NSCLC患者易发生脑转移,而ALK靶向抑制剂相对于一线化疗对脑转移有更好的疗效。但经第一代ALK抑制剂治疗后患者易耐药,进而出现颅内进展,第二代和第三代ALK抑制剂可增强其对中枢神经系统的渗透性、提高其到达靶点后的结合力,对脑转移癌有较好的治疗效果。本文回顾靶向治疗在*ALK*阳性NSCLC脑转移患者治疗方面取得的进展,并对目前存在的问题及未来发展方向进行探讨。

[关键词] 间变性淋巴瘤激酶;非小细胞肺癌;脑转移;靶向治疗
中图分类号] R734.2;R730.51 [文献标识码] A [文章编号] 1007-385X(2018)04-0431-06

肺癌是全球发病率和病死率最高的恶性肿瘤[1],其中非小细胞肺癌(non-small cell lung cancer,NSCLC)占约85%。NSCLC极易发生脑转移,导致患者出现严重的神经功能损伤和认知障碍,危及患者生命。约9%的NSCLC患者首诊时已发生脑转移[2-3],而在NSCLC疾病进程中,即便经过现有标准的治疗,最终仍有40%的患者会发生脑转移。当前肺癌脑转移患者的治疗是在全身治疗的基础上,进行针对脑转移的治疗包括手术、全脑放疗(whole brain radiotherapy,WBRT)、立体定向放射治疗(stereotactic radiotherapy,SRT)和以铂类为主的化疗在内的多学科综合治疗[4-5]。尽管如此,NSCLC脑转移患者预后仍不容乐观,中位生存期约为7个月,而颅内多部位转移者仅3个月[6]。

随着对疾病发病机制的逐步深入研究,分子靶向治疗已成为NSCLC脑转移患者的重要治疗模式之一[4,7]。间变性淋巴瘤激酶(anaplastic lymphoma kinase,*ALK*)基因重排是继表皮生长因子受体(*EGFR*)基因突变之后被发现的另一个重要治疗靶点[8]。NSCLC患者中*ALK*融合基因阳性率约2%~7%[9-11],多见于较年轻、从不或很少吸烟的腺癌患者[9]。酪氨酸酶抑制剂(tyrosine kinase inhibitor, TKI)克唑替尼(crizotinib)基于其良好疗效和耐受性成为*ALK*阳性晚期NSCLC一线治疗手段[12]。尽管疗效显著,多数患者在1年内仍不可避免发生获得性耐药[12-14],且40%~50%首先表现为颅内进展[13,15]。为了更好地控制NSCLC脑转移,近年来第二、三代ALK-TKI的开发与应用逐渐展现其各自的治疗效果。本文在此回顾了近年来靶向治疗在*ALK*阳性的NSCLC脑转移治疗方面取得的进展,并探讨目前存在的问题及未来发展方向。

1 *ALK*融合基因与NSCLC

*ALK*融合基因最早发现于间变性大细胞淋巴瘤(anaplastic large cell lymphoma,ALCL)[16],其编码的膜受体酪氨酸激酶(tyrosine kinase,TK)可激活Ras/MAPK/ERK、PI3K/AKT以及JAK3/STAT3等下游信号通路。NSCLC患者中*ALK*融合基因阳性率约2%~7%[9-11]。目前已发现超过20种ALK的融合蛋白[17],其中最早发现同时也是最常见的融合基因是*EML4-ALK*[18-19](表1)。目前ALK的检测以FISH、IHC以及RT-PCR为主[20],二代测序因其快捷全面的特点,有助于发现ALK新的融合突变形式,尽管价格相对昂贵,也逐渐成为主流检测方式之一[21]。另外,

[基金项目] 国家自然科学基金资助项目(No. 81572501, No. 81101908),海军军医大学大学生创新基金资助项目(No. ZD2017001)。Project supported by the National Natural Science Foundation of China (No. 81572501, No. 81101908) and the Innovation Training Program of Navy Medical University (No. ZD2017001)

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通过液体活检手段检测循环肿瘤DNA、循环肿瘤细胞的技术也在逐渐发展起来。*ALK*融合突变阳性的NSCLC患者使用ALK-TKI治疗可以获益，但治疗过程中，*ALK*融合基因的激酶结构域易出现L1196M、C1156Y和F1174L等点突变而产生获得性耐药[4,21]，继而发生肿瘤的神经系统转移。因此如何应对该种耐药机制以及如何进行后续用药是*ALK*阳性的NSCLC患者治疗所面临的困境。

表1 NSCLC中常见的*ALK*基因融合形式

与*ALK*相融合的基因	所在基因位点	融合基因	参考文献
TPR	1q31.1	*TPR-ALK*	[22]
*EML4**	2p21	*EML4-ALK*	[18]
TFG	3q12.2	*TFG -ALK*	[23]
PTPN3	9q31	*PTPN3-ALK*	[24]
KIF5B	10p11.22	*KIF5B-ALK*	[25]
KLC1	14q32.3	*KLC1-ALK*	[26]

*NSCLC中最常见的融合基因，其还有v1、v2、v3a/b等多种突变体形式[27]

2 *ALK*阳性NSCLC脑转移的特点

*ALK*阳性NSCLC患者的脑转移发生率约为20%~30%[12,28-30]，治疗过程中脑转移发生率60%~90%[7,31]。在靶向治疗时代之前，NSCLC脑转移患者预后极差，中位生存期3~15个月不等，其预后与病灶单发与否、年龄、KPS评分及有无颅外病灶密切相关[6,31]。相对*EGFR*突变的NSCLC脑转移患者，ALK阳性患者预后更好，生存期更长[32-33]，经放疗后中位生存期可延长至26个月。值得注意的是，相对于ALK靶向抑制剂，脑转移的病灶多发与否、选择WBRT或SRT都不是影响预后的重要因素，更有研究[34-35]表明，WBRT对于NSCLC脑转移患者收效甚微。

如何治疗NSCLC脑转移患者是当前亟待解决的问题，约50%的患者需接受1次以上脑放疗，25%甚至需要接受3次及以上的颅内放疗[20]。因此*ALK*阳性脑转移治疗需要多学科合作，且更需要针对于靶向ALK的药物对因治疗。

3 靶向ALK的酪氨酸酶抑制剂

3.1 第一代ALK靶向抑制剂

克唑替尼是第一代ALK靶向抑制剂的代表药物，是一种同时靶向c-MET和ROS酪氨酸激酶的小分子抑制剂[12,36]，是目前*ALK*阳性NSCLC患者的首选治疗方案。研究[12]表明，相较于传统一线化疗方案（培美曲塞联合铂类药物），克唑替尼治疗ALK阳性NSCLC患者的疾病控制率（disease control rate，DCR）明显优于化疗组（中枢神经系统DCR 56% *vs* 25%）。对*ALK*阳性脑转移患者进行的回顾性研究PROFILE 1005和PROFILE 1007[37]中，在无症状脑转移的*ALK*阳性NSCLC患者队列中，克唑替尼治疗后DCR达56%~62%；在脑转移病灶经治或未治的患者中，克唑替尼治疗后在中枢神经系统的客观缓解率（ORR）达18%~33%。然而对于不论有无脑转移的患者，中枢神经系统仍然是克唑替尼获得性耐药的主要部位：71%有脑转移的患者及27%无脑转移的患者最终报告了颅内病灶。然而，亦有研究[38]表明脑转移病灶对克唑替尼不敏感，其原因可能与血脑屏障导致克唑替尼通过率低有关[20]。靶向药物都有一个短板，就是易发生耐药，使用克唑替尼的患者往往在1~2年内出现耐药，以中枢神经系统的复发进展较为常见，目前发现其耐药主要为ALK激酶区突变即*ALK*融合基因拷贝数扩增所致[39]，此时则需要采用第二代、三代ALK-TKI进行进一步治疗。

3.2 第二、三代ALK靶向抑制剂

艾乐替尼（alectinib）是一个具有高度选择性的第二代ALK抑制剂，可阻断导致对克唑替尼耐药的L1196M突变，在*ALK*阳性的NSCLC治疗中显示出了对全身和中枢神经系统的疗效[40-41]。一项I/II期研究[42]治疗克唑替尼耐药的*ALK*阳性NSCLC，21例基线存在脑转移，脑脊液和血浆游离药物浓度呈正相关，说明新一代ALK抑制剂通过血脑屏障的能力明显增加。在最近一项三期临床试验[43]中，研究人员在未经治疗的晚期*ALK*阳性的NSCLC患者（包括无症状的脑转移患者）中比较艾乐替尼与克唑替尼的疗效，在艾乐替尼治疗组共有18例（12%）患者存在中枢神经系统进展事件，而在克唑替尼组有则68例（45%）（HR 0.16, 95%CI 0.10~0.28, P<0.001）。

色瑞替尼（ceritinib）是用于治疗ALK突变阳性、经克唑替尼治疗后疾病进展或不能耐受的转移性NSCLC患者的第二代ALK抑制剂，其有效率约为克唑替尼的20倍，且对克唑替尼耐药的突变基因均有效[44]。最近公布的ASCEND-4的三期临床试验结果显示，相较于一线化疗，对于存在脑转移的NSCLC患者，色瑞替尼治疗达到了高效、持续的系统缓解以及较高的颅内缓解（46.3% *vs* 21.2%），同时延长了无进展生存期（PFS）（10.7 *vs* 6.7个月）。因其在脑转移患者治疗中取得的突破性进展，FDA加速批准了色瑞替尼的补充新药申请的优先评审权，并作为ALK阳性的转移性NSCLC患者的一线治疗方案[45]。

布格替尼（brigatinib）是一种可逆的EGFR/ALK双重抑制剂，对ALK-TK继发性突变和其他ALK耐

药突变均有效，且表现出极强的中枢神经系统渗透能力[46]。作为克唑替尼的接力靶向药，研究[47]表明，经布格替尼接力治疗后，全身和颅内肿瘤反应率都很显著，低剂量组（90 mg）颅内缓解率42%，中位PFS 9.2个月；高剂量组颅内缓解率67%，中位PFS是12.9个月，首次使克唑替尼耐药患者PFS长达1年以上[47]。因布格替尼的广谱抗耐药，FDA近期加速批准其上市，用以接力克唑替尼耐药的肺癌患者。

劳拉替尼（lorlatinib）是第三代ALK抑制剂，属于ALK/ROS1双靶点抑制剂，可有效对抗各类ALK继发的耐药基因突变，有较强的中枢神经系统渗透性[48-49]，保持脑组织中较高的血药浓度。目前同样已由FDA批准上市。用于二线治疗*ALK*阳性的转移性NSCLC[50]。

表2 目前已被FDA批准的ALK靶向抑制剂

名称	代号	靶点	可靶向的耐药突变	易发生的继发耐药突变	BBB通过率	参考文献
克唑替尼（Crizotinib）	第一代	*ALK* *ROS1* *c-MET*	L1198F	I1151Tins L1152P/R C1156Y/T I1171T/N/S F1174C/L/V V1180L L1196M G1202R S1206C/Y E1210K G1269A/S	较弱	[12,36,51-52]
艾乐替尼（Alectinib）	第二代	*GAK* *LTK* *RET* *ALK*	L1152P/R C1156Y/T F1174C/L/V L1196M S1206C/Y G1269A/S	I1171T/N/S V1180L G1202R	可通过	[52-54]
色瑞替尼（Ceritinib）	第二代	*ROS1* *IGF1R* *IR* *ALK*	I1171T/N L1196M S1206C/Y G1269A/S	I1151Tins L1152P/R C1156Y/T F1174C/L/V G1202R	可通过	[44,52]
布格替尼（Brigatinib）	第二代	*EGFR* *ALK*	I1151Tins L1152P/R C1156Y/T F1174C/L/V L1196M G1202R G1269A/S	G1202R E1210K +S1206C E1210K +D1203N	强	[52,55-57]
劳拉替尼 Lorlatinib	第三代	*ROS1* *ALK*	I1151Tins L1152P/R C1156Y/T I1171T/N/S L1196M G1202R S1206C/Y E1210K G1269A/S	L1198F +C1156Y	强	[48,51-52]

4 结 语

出现脑转移的晚期NSCLC患者的治疗方案，需考虑进行肿瘤内科、放疗科、神经外科等参与的多学科讨论，应该在全身治疗的基础上，进行针对脑转移的治疗，包括手术、全脑放疗、立体定向放射治疗、化

疗和分子靶向治疗在内的多学科综合治疗，其目的是治疗转移病灶、改善患者症状、提高生活质量，最大程度地延长患者生存时间。

随着对疾病机理和药物研究的不断深入，ALK抑制剂的作用与功能也在逐渐完善。对第一代酪氨酸酶抑制剂克唑替尼，尽管多数患者仍在1年内不可避免地发生获得性耐药并出现颅内进展，但近年来第二、三代ALK-TKI的开发与应用逐渐展现其各自的治疗效果，且还出现了ALK-TKI“轮回”的现象：即经过克唑替尼耐药后的NSCLC患者经劳拉替尼接力治疗后再次对克唑替尼敏感[51]。尽管基于目前研究结果，ALK-TKI对控制*ALK*阳性的NSCLC脑转移有一定的治疗效果，但因研究开展相对较少，如何联合放疗方案更好的达到治疗目的仍然需要更多的临床实践和探索。

对ALK靶向抑制剂进行修饰以克服常见的耐药性、增强其对中枢神经系统的渗透性、提高其到达靶点后的结合力及效果的研究越来越多。相信在不久的将来，基于肿瘤基因组研究，将分子靶向治疗与传统放化疗及其他治疗模式相结合的个体化综合治疗将是未来探索综合治疗NSCLC脑转移的重要方向。

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［收稿日期］ 2017-12-07　　［修回日期］2018-03-23
［本文编辑］ 黄静怡